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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GRASER, JENNIFER E	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 05/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/386,709	BRAYDEN, DAVID J.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-25,27-31,33,35,38,39 and 41-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-25,27-31,33,35,38,39 and 41-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed on 2/13/04 has been entered. Claims 21-25, 27-31, 33, 35, 38, 39, 41, 42 and 43 are currently under examination.

Priority

1. If applicant desires priority under 35 U.S.C. 119(e) based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet. It is noted that reference to provisional application, U.S. Serial No. 60/098,759 does not appear in the application data sheet. Accordingly, the specification should be amended to include reference to said application.

Specification

2. The amendment filed 2/13/04 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

Figure 7 is new matter. The application was originally filed with only 6 Figures; Figures 1-6. Applicant is required to cancel the new matter in the reply to this Office Action. Alternatively, if Applicants can demonstrate by 'return/receipt postcard' or other evidence that the application was filed with seven figures, then Figure 7 will be allowed into the specification.

Specification

3. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Originally filed claims 6 and 12 recite a method "wherein the microparticles comprise at least 2 subpopulations of microparticles, each subpopulation comprising a different antigen entrapped or encapsulated by a biodegradable polymer". However, the instant specification does not provide proper antecedent basis for this claim language. The specification should be amended, provided no new matter is added, to include support for this claim language.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 21-25, 27-31, 33, 35, 38, 39, 41, 42 and 43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification is not enabled for 'methods of inducing a protective immune response wherein said method comprises orally administering to a subject therapeutically effective amounts of at least a first and second subpopulation of micro[nano]particles, wherein each of said micro[nano]particles comprises an antigen entrapped or encapsulated by a biocompatible, biodegradable polymer, and wherein the

antigen in the micro[nano]particles of the first subpopulation is different than the antigen in the micro[nano]particles of the second subpopulation...". The specification fails to provide any description of such a method, nor are any results provided for such a method. The specification has demonstrated with challenge results that a single antigen encapsulated in a microparticle and administered orally provides protection against the wild-type organism and have also demonstrated that two antigens encoded together within the same microcapsule and orally administered can also provide protection.

However, the specification is silent on the oral administration of two subpopulations of microparticles each containing a different antigen. The prior art teaches that the vaccine art is highly unpredictable. It has also taught that multivalent vaccines are unpredictable and often times less effective than a single antigen vaccine in providing protection due to antigenic competition between the two antigens. Applicants stated in the Amendment filed February 26, 2002 on page 6 that support and enablement for this method could be found in Examples 7 and 8. However, a recent review of Examples 7 and 8 does not describe "a first and second subpopulation of microparticles, wherein each of said microparticles comprises an antigen entrapped or encapsulated by a biocompatible, biodegradable polymer, and wherein the antigen in the microparticles of the first subpopulation is different than the antigen in the microparticles of the second subpopulation". Example 7 teaches microparticles with Ptd and FHA together in a single microparticle, not each in their own microparticle as required by the claim. The Example refers to 4 different test groups in which the first

group received control PLG (empty PLG microparticles), the second group received Ptd entrapped in PLGA microparticles, the third group received Ptd SOLUTION and the fourth group received microparticles containing both Ptd and FHA entrapped in the same microparticles (i.e., 100ug of each antigen not two different subpopulations of microparticles). Results for the microparticles containing both antigens are provided. Figure 6 further demonstrates the results which do not include an experiment in which a first and second subpopulation of microparticles, each containing a different antigen are administered to a mouse.

Example 8 also fails to provide enablement for this limitation. Example 8 describes three different groups of mice. The first group received Ptd and FHA in saline. The second group received Ptd and FHA together in the same microparticles. The third group received empty nanoparticles. No results of immunization experiments which administered two subpopulations containing different antigens are provided, nor does the specification mention any such experiments. The entire body of the example refers to Ptd and FHA together in solution or Ptd and FHA entrapped in PLGA. There is no mention of two different subpopulations of microparticles, each containing a different antigen.

Page 5, lines 28-29, recites that "[p]referably, the microparticles or nanoparticles contain at least two *B.pertussis* antigens, such as inactivated *B.pertussis* toxin or FHA". No mention is made of two subpopulations of microparticles each containing a different antigen. Which further supports that the Ptd and FHA antigens used in Examples 7 and

8 were entrapped in the same microparticles. No mention is made of the antigens being separately encapsulated and in two different populations.

Further, as pointed out by Applicants in their response of July 30, 2003, Shahin et al teach that administration of microencapsulated FHA fails to stimulate a protective mucosal response via the oral route yet were successful with the intranasal administration of microencapsulated FHA. Jones et al indicate success with oral administration of a single population of microencapsulated fimbriae antigen. Since Shahin et al were unable to produce an adequate immune response after oral immunization with microencapsulated FHA, the same vaccine which is being used in the invention, it is unclear that methods which use microparticles containing FHA as recited in claims 25, 31 and 33, and would work as oral vaccines. It is even more unpredictable that two subpopulations of microencapsules containing different antigens would provide success. Given the unpredictability in the prior art coupled with the claims requirement for 'protection' results from challenge experiments using the methods as instantly claimed are required to support enablement. The instant specification fails to describe the instantly claimed methods and further fails to provide any results from experiments which use a first and second subpopulation of microparticles each containing a different antigen and co-administered orally.

Applicants have referred to results that show that PT+FHA gives better than 2 Log10 units improvement over PT alone; however, these results are not commensurate in scope with the claimed invention because the PT and FHA were encapsulated in the same microcapsule and not in separate microcapsules as required by the claim. As the

prior art has demonstrated, this difference is significant and appears to be what Applicants deem distinguishing over the prior art.

The specification provides no results for the scope of the current claims; i.e., methods of inducing a protective immune response wherein said method comprises orally administering to a subject therapeutically effective amounts of at least a first and second subpopulation of micro[nano]particles, wherein each of said micro[nano]particles comprises an antigen entrapped or encapsulated by a biocompatible, biodegradable polymer, and wherein the antigen in the micro[nano]particles of the first subpopulation is different than the antigen in the micro[nano]particles of the second subpopulation', nor does it provide results for any multivalent vaccines with antigens other than the pertussis antigens. Additional evidences may be provided to enable the scope of the invention.

Response to Applicants' Arguments:

In the Amendment filed February 26, 2002, Applicant has stated that support for a method comprising two subpopulations of micro/nanoparticles each containing a different antigen is found in Examples 7 and 8 of the application.
On page 21, lines 4-5, Example 7 recites: "PTd-FHA-PLG (100 ug of each of Ptd and FHA entrapped in PLGA microparticles)" . The Examiner has interpreted this phrase to mean 100 ug of Ptd and 100 pg of FHA encapsulated within the same microparticle. In contrast, Applicant asserts that this phrase refers to a first subpopulation of 100 ug of Ptd entrapped in PLGA microparticles and a

second subpopulation of 100 ug of FHA entrapped in PLGA microparticles. Applicants have argued that Figure 7, not part of the instant application, show results with Ptd and FHA in different microparticles. This has been carefully considered but is not deemed persuasive. The key to Figure 7 recites "Ptd+FHA-PLGA". 'PTd+FHA" is read as the two antigens together. Two separate subpopulations of microparticles, each containing a different antigen would be written as "PTd-PGLA" and "FHA-PGLA". There is nothing else in the Figure that supports the conclusion that it is two separate populations of microparticles. Further, the graph shows 3 lines; control; soluble Ptd+FHA' and "Ptd+FHA-PLGA". If Ptd and FHA were in different microparticles, there would be different lines representing their different immune responses. These different antigen containing microparticles would not have the same exact immune response, i.e, represented by the same graph line.

With respect to Example 8, Treatment 2 recites: "Ptd+FHA in PLGA (blend of 100ug each of antigen entrapped in nanoparticles according to Example 4)". A "*blend of 100ug each of antigen*" is a mixture of 100ug each of the two antigens, as supported by the use of "Ptd+FHA in PGLA". Once again, if the antigens were in different microparticles there would not be a *blend of 100ug each of antigen*, and it would be written as Ptd-PGLA and FHA-PGLA; not Ptd+FHA-PGLA. Applicants have further argued that Example 8 on page 24, lines 11 to 12, which recites: "They reveal a high level of protection in animals orally immunised with a blend of nanoparticles entrapping Ptd and FHA respectively". Applicants argue that the use of the term "respectively" in this sentence indicates nanoparticles entrapping either Ptd or FHA, not Ptd and FHA.

This has been carefully considered but is not deemed persuasive. The Examiner does not view this language as indicating that the antigens are entrapped in separate nanoparticles. In fact, a few lines after this sentence beginning at line 26, it is recited "[t]he efficacy of the nanoparticle (note no plural) entrapped FHA **and** PTd is roughly comparable with that observed for the solvent evaporated microparticles delivered by the oral route according to [Example 7]. This further implies that the antigens are entrapped, in a blend, within the same microparticle. As stated above, the key to Figure 7 recites "Ptd+FHA-PLGA". 'PTd+FHA" is read as the two antigens together. Two separate subpopulations of microparticles, each containing a different antigen would be written as "PTd-PGLA" and "FHA-PGLA". There is nothing else in the Figure that supports the conclusion that it is two separate populations of microparticles. Further, the graph shows 3 lines; control; soluble Ptd+FHA' and "Ptd+FHA-PLGA". If Ptd and FHA were in different microparticles, there would be different lines representing their different immune responses. These different antigen containing microparticles would not have the same exact immune response, i.e, represented by the same graph line. Accordingly, the specification is not enabled for the claimed methods.

Prior Art Rejections

6. Claims 21-25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jones et al (Infect.Immun., 1996, 64(2): 489-494) in view of Eckhardt et al (US 5,897,867) in further view of Singh et al (Vaccine, 1998, 16(4): 346-352) and Shahin et al. (Infect.Immun., Apr.1995, 63(4): 1195-1200) for the reasons set forth in the Office Action mailed 9/11/03.

7. Claims 28-31, 33, 35 and 43 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Jones et al (Infect.Immun., 1996, 64(2): 489-494) in view of Eckhardt and Singh et al (Vaccine, 1998, 16(4): 346-352) and Shahin as set forth above and further in view of O'Hagan et al (US 5,603,960) for the reasons set forth in the Office Action mailed 9/11/03.

8. Claims 38 and 41 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Jones et al (Infect.Immun., 1996, 64(2): 489-494) in view of Eckhardt, Shahin and Singh as applied to claims 21-25 and 27 above, and further in view of Andrianov (US Patent No. 5,807,757) for the reasons set forth in the Office Action mailed 9/11/03.

9. Claims 39 and 42 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Jones et al (Infect.Immun., 1996, 64(2): 489-494) in view of Eckhardt, Shahin, Singh et al and O'Hagan et al (US 5,603,960) as applied to claims 28-31, 33 and 35-37 above, and further in view of Andrianov for the reasons set forth in the Office Action mailed 9/11/03.

Response to Applicants' Arguments:

Applicants argue that there is no reasonable expectation that a combination of Jones et., Eckhardt et al., Singh et al., and Shahin et al. would be successful. Furthermore, the teaching to make the claimed combination as well as the expectation of success is not found in any of the cited publications as required by MPEP 2143. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208

USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is noted that the present specification provides no results from a method comprising orally administering to a subject therapeutically effective amounts of at least a first and second subpopulation of micro[nano]particles, wherein each of said micro[nano]particles comprises an antigen entrapped or encapsulated by a biocompatible, biodegradable polymer, and wherein the antigen in the micro[nano]particles of the first subpopulation is different than the antigen in the micro[nano]particles of the second subpopulation. Applicants argument against unpredictability is invalid without results from their own experiments.

Jones et al teach that fimbriae from *Bordetella pertussis* encapsulated in poly(lactide-co-glycolide) microparticles of a size appropriate for uptake by the immune inductive tissues of the gastrointestinal tract could *protect* mice from *B.pertussis* respiratory infection upon oral administration (abstract). It is disclosed that the mean diameter of the microparticles was 2.04um, i.e., less than 3um, with 90% of microparticles having diameters within the narrow range of 0.8 to 5.3 um (see page 490, Results section). Jones teaches that six weeks after immunization, all immunized animals were protected against intranasal challenge with live *B.pertussis* (abstract). Applicants' remarks on page 19, paragraph 2, of the Amendment are incorrect. The passage they refer to is not Jones et al. discussing what occurred in the present study, but is a review of the prior art. Jones states in paragraph 1 of the 'Discussion" section on page 491, "that [the] results presented here convincingly show the effectiveness of microencapsulation as a means of delivering antigens by the oral route and the ability of

orally administered microencapsulated fimbriae to elicit specific and systemic mucosal immune responses". Applicants have taken statements out of context and not reviewed the reference as a whole.

With respect to Applicants arguments concerning the teachings of Shahin et al., Shahin teaches that subpopulations of different microencapsulated antigens from *B.pertussis* allow for a better immune response than a single microencapsulated population intranasally. Although Shahin teaches that success was not found with oral administration of single population of microencapsulated FHA antigen, the reference teaches this is most likely due to the amount of microcapsules administered orally since it was well known in the prior art that less than 1% or an oral dose of DL-PLG microspheres successfully reaches the Peyer's patches. It is noted that Shahin et al did not attempt to increase the dose of microcapsules orally administered, nor did Shahin try orally administering three subpopulations of all three pertussis antigens as was done intranasally. Shahin is cited to show that it was well known that administration of subpopulations of different microencapsulated antigens from *B.pertussis* allow for a better immune response than a single microencapsulated. Shahin teaches that if a greater volume of microcapsules were administered orally, that most likely the immune response would be sufficient. Shahin does not teach against oral administration, but instead teaches that it requires a greater amount of microcapsules than intranasal administration. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413,

208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is (703) 872-9306 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

Jennifer Graser 5/3/04
Jennifer Graser
Primary Examiner
Art Unit 1645